## REMARKS

## STATUS

Claims 1-23 were originally filed. By the present amendment, claims 2, 8, 14 and 21 have been cancelled, and new claims 24-26 have been added. Accordingly, it is now claims 1, 3-7, 9-13, 15-20 and 22-26 which are at issue.

## THE OFFICE ACTION

In the Office Action mailed July 11, 2003, claims 1-23, all claims then pending, were rejected.

Claims 1, 3, 7, 12, 13, 15, 16 and 17 were rejected under 35 U.S.C. §102 as being anticipated by U.S. Patent No. 4,686,211 of Hara et al.

Claims 4-6 were rejected 35 U.S.C. §103 in view of Hara et al.

Claims 2 and 14 were rejected under 35 U.S.C. §103 as being unpatentable over Hara et al. and further in view of U.S. Patent No. 4,937,078 of Mezei et al.

Claims 1-23 were rejected under 35 U.S.C. §103 as being unpatentable over U.S. Patent No. 6,391,869 of Parks et al.

Claims 1-23 were rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 6,159,944 of Fogel in view of Parks et al.

Claims 2, 14 and 21 were rejected under 35 U.S.C. §103 as being unpatentable over Parks et al. or, in the alternative, in view of U.S. Patent No. 6,159,944 of Fogel in combination with Parks et al.

Applicant thanks the Examiner for the search, for the Office Action, and for the thorough explanation of the basis of the rejections.

THE REJECTION UNDER 35 U.S.C. §102

Claims 1, 3, 7, 12, 13, 15, 16 and 17 were rejected under 35 U.S.C. §102 as being anticipated by U.S. Patent No. 4,686,211 of Hara et al. By the present amendment, Applicant has incorporated the subject matter of claim 2 into independent claim 1. Claim 2 was not subject to any rejection based on Hara et al., and claim 1 as well as claims 3-7 and 9-11 now overcome the rejection based upon Hara et al. Likewise, independent claim 12 has been amended to incorporate the subject matter of claim 14 therein. Claim 14 was not subject to any rejection based upon Hara et al. and claim 12 as well as claims 13 and 15-18 dependent thereupon overcome any rejection based upon Hara et al.

THE REJECTIONS UNDER 35 U.S.C. §103

I. Claims 4-6 were rejected under 35 U.S.C. §103 as being unpatentable over Hara et al. In view of the amendment to claim 1, Applicant respectfully submits that this rejection is moot.

II. Claims 2 and 14 were rejected under 35 U.S.C. §103 as being unpatentable over Hara et al. and further in view of U.S. Patent No. 4,937,078 of Mezei et al. Applicant respectfully submits that in view of the present amendments, this rejection is overcome. Claims 2 and 14 originally stated that the carrier used in formulating the compositions of the present invention included liposomes and that the lidocaine, or other topical anesthetic, was disposed within the liposomes. In formulating the rejection, the Examiner has cited to the Mezei et al. patent for the teaching of a formulation in which a topical anesthetic is incorporated into liposomes. The Examiner has further held that in view of the teaching of Mezei et al., it would be obvious to one of

skill in the art to incorporate the lidocaine of the Hara et al. formulation into liposomes so as to approximate the present invention.

Applicant respectfully submits that in view of the present amendments, this rejection is overcome. By the present amendment, Applicant has incorporated the subject matter of originally filed claims 2 and 14 into claims 1 and 12, respectively. Both of these original dependent claims stated that the lidocaine or topical anesthetic is disposed within the liposomes. However, in making the amendments to claims 1 and 12, Applicant has further specified that the L arginine is disposed in the continuous phase of the liposomal preparation. This language clearly distinguishes the present formulation over any formulations shown or suggested in Hara et al. or Mezei et al.

The sole teaching of Mezei et al. is directed to formulations in which a topical anesthetic is disposed in a liposomal phase of a preparation. Hara et al. does not show any liposomal preparation at all. Furthermore, the real teaching of Hara et al. is all directed to the use of a particular class of organophosphate salts as permeation enhancers for facilitating the transdermal delivery of various medications. A preferred group of organophosphate salts utilized in Hara et al. is derived by reacting the organophosphate material with an alkaline amino acid such as arginine. In the specific formulation referred to by the Examiner, lidocaine is the therapeutically effective agent, and the arginine-derived organophosphate salt is the permeation enhancer. While the Examiner has stated that it would be obvious to one of skill in the art to incorporate the lidocaine of Hara et al. into the liposomes of Mezei et al., in view of Mezei et al.'s teaching that doing so enhances the effectiveness of the lidocaine, there is no teaching or suggestion which would lead one of skill in the art to prepare a formulation in which arginine was disposed in a continuous phase outside of the liposomes. First of all, all teaching in

Mezei et al. is that incorporation of active species into liposomes enhances their activity, and all teaching in Hara et al. is that the organophosphate salt is a permeation enhancer for the active drug species. If one of skill in the art were to read the two references in combination, that person would expect that the permeation enhancer, namely the organophosphate salt, should also be incorporated into the liposomes, since its function is to enhance permeability of the lidocaine. In any case, there is no teaching or suggestion in Mezei et al. that it would be desirable or beneficial to include further active species in the formulations of Mezei et al. which species are disposed outside of the liposomes.

The present application, as originally filed, specifically teaches formulations in which a topical anesthetic such as lidocaine is disposed in a liposomal phase of a carrier vehicle and arginine is disposed in the continuous phase. Separating the components provides a formulation which is highly effective and also has very good stability and shelf life. Applicant respectfully submits that in view of the amendments submitted herewith, the rejections under 35 U.S.C. §103 based upon the combination of Hara et al. and Mezei et al. are overcome.

III. Claims 1-23 were rejected under 35 U.S.C. §103 as being unpatentable over U.S. Patent No. 6,391,869 of Parks et al. Parks et al. discloses a class of compositions for the treatment of anorectal disorders. These compositions include a first active ingredient which is a NO donor. Among some of the listed NO donor materials is arginine. The Parks et al. formulations further include a second agent which is used in combination with the NO donor. The second agent is a cAMP or cGMP modulator and its purpose is to moderate adverse side effects of the NO donor. The second agent can be selected from a large grouping of generic materials, and these are set forth in the passage

running from column 9, line 48 to column 10, line 8. It is notable that in no instance is this grouping of second agents described as including any topical anesthetic. The Parks et al. patent does go on to show formulations having auxiliary agents which can include topical anesthetics such as lidocaine. The Examiner notes that Parks et al. does suggest that the formulations thereof could be incorporated into vehicles which include liposomes. The Examiner acknowledges that Parks et al. does not show the specific compositions and formulations of the present invention; but, is of the opinion that they would be obvious in view of the teaching thereof.

Applicant respectfully submits that the disclosure of Parks et al. does not show or suggest formulations of the present invention; furthermore, in view of the amendments submitted herewith, all rejections based upon Parks et al. are overcome.

With regard to the issue of the liposomal carrier: Parks et al. does have a brief teaching at column 17 of a large number of carriers, specifically including:

> Powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches, suppositories and liposomal preparations.

Applicant respectfully submits that this broad teaching, in the absence of any further suggestion, and further in view of the fact that none of the examples show any liposomal preparation, is insufficient to suggest to one of skill in the art the desirability of formulating the compositions of the present invention. In any case, the claims as now amended are directed to preparations that are not only liposomal based, but preparations in which the lidocaine or topical anesthetic portion of the composition is disposed within the liposomes and the arginine portion of the composition is disposed in the continuous phase. There is absolutely no teaching or suggestion in Parks et al. of compositions of

this type, and Applicant respectfully submits that in view of these amendments, the rejections based upon Parks et al. are overcome.

IV. Claims 1-23 were rejected under 35 U.S.C. §103 as being unpatentable over U.S. Patent No. 6,159,944 of Fogel taken in view of Parks et al. Fogel was cited for its teaching of compositions for treating hemorrhoids and like conditions, which compositions are comprised of nitroglycerine and lidocaine. Parks et al. is cited for its teaching of the equivalency of nitroglycerine and lidocaine as NO donors for the treatment of anorectal disorders. On this basis, the Examiner is of the opinion that one of skill in the art could, in view of the teaching of Parks et al., substitute arginine for nitroglycerine in Fogel and approximate the presently claimed invention.

Applicant respectfully submits that this reference is essentially cumulative of the rejection under 35 U.S.C. §103 based upon the teaching of Parks et al. alone, and in view of the amendments to the claims, this rejection is likewise overcome. Specifically, there is no teaching in Fogel of any liposomal preparation, much less a preparation of arginine and lidocaine. While Parks et al. does briefly mention liposomal preparations, there is no teaching or suggestion in Parks et al. of the specifically claimed liposomal preparations in which lidocaine is disposed within the liposomal phase and arginine in the continuous phase. In view of the shortcoming of the prior art, and in consideration of the benefits achieved by the compositions of the present invention, Applicant respectfully submits that this rejection is overcome.

V. Claims 2, 14 and 21 were rejected under 35 U.S.C. §103 as being unpatentable over Parks et al. in view of Mezei et al.; or, in the alternative, Fogel and Parks et al. in view of Mezei et al. Applicant respectfully submits that in view of the amendments made herein, these rejections are likewise overcome.

As discussed with the rejections in Section II herein above, the Mezei et al. reference teaches liposomal formulations in which lidocaine or the like is disposed within a liposomal phase. Both Parks et al., or the combination of Parks et al. and Fogel, have been cited for the alleged showing of a formulation of arginine and lidocaine in a liposomal carrier. As noted above, the claims as now amended clearly recite that the lidocaine, or topical anesthetic portion of the formulation of the present invention, is disposed in the liposomal phase of the carrier and arginine is disposed in the continuous phase. There is no teaching in Mezei et al. or in Parks et al. or Fogel of formulations of this type. Furthermore, one of skill in the art having reference to Mezei et al. would be inclined to incorporate both the lidocaine and the arginine into the liposomal phase, since Mezei et al. teaches that enhancement of activity of such pharmaceuticals occurs when they are present in a liposomal phase. As such, the prior art actually teaches away from the principles of the present invention. In view of these remarks and the amendments to the claims, Applicant respectfully submits that these rejections are overcome.

THE NEW CLAIMS

I. New claims 24-26 are patentable over all of the prior art of record. New claim 24 is cast in a partially closed format and is directed to a composition consisting essentially of L arginine which is in the form of the free amino acid, a local anesthetic and a pharmaceutically acceptable carrier. The subject matter of this claim is novel and non-obvious over all of the prior art of record. The Hara et al. patent discloses a composition based upon lidocaine and a salt of a dialkyl phosphate. In specific examples, the salt is the salt of L arginine. Nowhere in Hara et al. is there shown or suggested any compositions which employ free acids much less compositions having L arginine in its free amino acid form. Given the fact that Hara et al. employs L arginine

as one of a number of possible salt formers for the therapeutically utilized dialkyl phosphate ester clearly precludes any teaching or suggestion of employing the free amino acid in any compositions.

Claim 24 is likewise patentable over the Parks et al. patent. As discussed above, Parks et al. discloses compositions based upon a NO donor such as arginine together with a second agent which functions to modulate the levels of cAMP or cGMP. These second agents are extensively detailed in the Parks et al. patent, and do not include topical anesthetics; although, Parks et al. does disclose compositions which may also include a topical anesthetic in combination with the foregoing two agents. Given that claim 24 is in "consisting essentially of" form, it clearly excludes the cAMP and cGMP agents. Furthermore, given the teaching in Parks et al. of the necessity for the cAMP and cGMP agents, one of skill in the art would not be motivated to eliminate these critical components from the Parks et al. formulations so as to approximate the present invention. Therefore, the subject matter of new claim 24 is not shown or suggested in Parks et al.

Likewise, the secondary references of Fogel and Mezei et al. which were used in combination with Parks et al. and/or Hara et al. in rejecting the originally filed claims, do not show or suggest the principles of the present invention. As the Examiner has acknowledged, neither of these references shows or suggests the combination of L arginine in the form of a free amino acid together with a local anesthetic. In view thereof, new claim 24 is patentable.

II. New claim 25 tracks original claim 1 except that it specifies that the L arginine is in the form of the free amino acid. For the reasons discussed above with reference to claim 24, this claim is clearly patentable over the teaching of Hara et al.

New claim 25 is likewise patentable over the teaching of Parks et al. taken either singly or in combination with any of the secondary references. As acknowledged by the Examiner, Parks et al. does not show Applicant's claimed compositional ranges. Furthermore, there is no showing or suggestion in the art which would lead one of skill to select the particular claim ranges. Therefore, new claim 25 is patentable.

III. New claim 26 is dependent upon new claim 25 and further specifies that the carrier comprises liposomes disposed in a continuous phase, and the lidocaine is disposed within the liposomes and the L arginine in the continuous phase. As discussed above with regard to the amended claims, the prior art does not show or suggest any composition having lidocaine disposed within liposomes and L arginine disposed in a continuous phase outside of the liposomes. New claim 26 is patentable over all of the prior art for the reasons set forth above.

## CONCLUSION

In view of the amendments and remarks submitted herewith, all claims are in condition for allowance. Any questions, comments or suggestions that the Examiner may have which would place the claims in still better condition for allowance should be directed to the undersigned attorney.

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AMENDMENTS TO THE CLAIMS

1. (Currently Amended) A topical composition comprising, on a weight basis:

0.1-18% of L arginine;

1-15% of lidocaine; and

a pharmaceutically acceptable carrier which includes liposomes disposed in a continuous phase; wherein said lidocaine is disposed within said liposomes, and said L arginine is in said continuous phase.

2. (Cancelled)

3. (Original) The composition of claim 1, wherein said lidocaine is present in a weight amount of 1-10%.

4. (Original) The composition of claim 1, wherein said lidocaine is present in a weight amount of 5%.

5. (Original) The composition of claim 1, wherein said L arginine comprises 0.1-3 weight percent of said composition.

6. (Original) The composition of claim 1, wherein said L arginine comprises, on a weight basis, 1% of said composition.

7. (Original) The composition of claim 1, wherein said L arginine is present as a salt.

8. (Cancelled)

9. (Original) The composition of claim 1, further including a topical corticosteroid.

10. (Original) The composition of claim 9, wherein said topical corticosteroid is hydrocortisone or a derivative thereof.

11. (Original) The composition of claim 1, further including a material selected from the group consisting of: diltiazem, indomethacin, piroxicam, naproxen, ibuprofen, sildenafil, allantoin, phenylephrine, combinations of the foregoing, and salts of the foregoing.

12. (Currently Amended) A composition for the treatment of anorectal disorders, said composition comprising: L arginine, a local anesthetic, and a pharmaceutically acceptable carrier which includes liposomes disposed in a continuous phase; wherein said local anesthetic is disposed within said liposomes, and said L arginine is in said continuous phase.

13. (Original) The composition of claim 12, wherein said local anesthetic is selected from the group consisting of: lidocaine, benzocaine, tetracaine, procaine,

mepivacaine, bupivacaine, prilocaine, ropivacaine, etidocaine, pramoxine, diclonine, phenacaine, and combinations thereof.

14. (Cancelled)

15. (Original) The composition of claim 12, wherein said L arginine is present as a salt.

16. (Original) The composition of claim 12, wherein said L arginine comprises, on a weight basis, 0.1-18% of said composition.

17. (Original) The composition of claim 12, wherein said topical anesthetic comprises, on a weight basis, 1-15% of said composition.

18. (Original) The composition of claim 12, further including a material selected from the group consisting of: diltiazem, indomethacin, piroxicam, naproxen, ibuprofen, sildenafil, allantoin, phenylephrine, combinations of the foregoing, and salts of the foregoing.

19. (Currently Amended) A method for treating an anorectal disorder in a patient, said method comprising applying to the affected area of said patient a composition comprising L arginine, ~~and~~ a local anesthetic and a pharmaceutically acceptable carrier comprising liposomes disposed in a continuous phase;

wherein, said local anesthetic is disposed within said liposomes, and said L arginine is in said continuous phase.

20. (Original) The method of claim 19, wherein said local anesthetic comprises lidocaine.

21. (Cancelled)

22. (Original) The method of claim 19, wherein said L arginine comprises, on a weight basis, 0.1-5% of said composition.

23. (Original) The method of claim 19, wherein said composition further includes a material selected from the group consisting of: diltiazem, indomethacin, piroxicam, naproxen, ibuprofen, sildenafil, allantoin, phenylephrine, combinations of the foregoing, and salts of the foregoing.

24. (New) A composition for the treatment of anorectal disorders, said composition consisting essentially of: L arginine which is in the form of the free amino acid, a local anesthetic, and a pharmaceutically acceptable carrier.

25. (New) A topical composition comprising, on a weight basis:

0.1-18% of L arginine which consists essentially of the free amino acid;

1-15% of lidocaine; and

a pharmaceutically acceptable carrier.

26. (New) The topical composition of claim 25, wherein said carrier comprises liposomes disposed in a continuous phase; and wherein said lidocaine is disposed within said liposomes, and said L arginine is in said continuous phase.